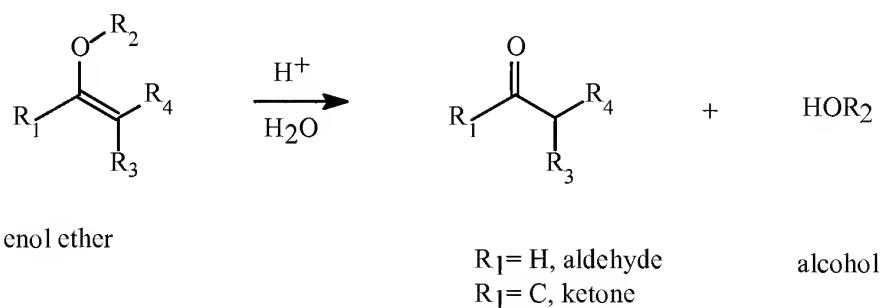


another carbon, i.e. an enol. Enols are unstable and rapidly convert to the carbonyl, i.e. the ketone or aldehyde. Enol ethers are stable, relative to enols, but under acidic aqueous conditions convert to alcohol and ketone or aldehyde. Depending on the structures of the carbonyl compound formed and the alcohol release, enol hydrolysis can be very pH-labile. In 5 general, hydrolysis to form ketones is much faster than the rate of conversion to aldehydes. For example the rate of hydrolysis of ethyl isopropenyl ether to form ethanol and acetone is ca. 3600 times faster than the hydrolysis of ethyl trans-propenyl ether to form ethanol and propanal.

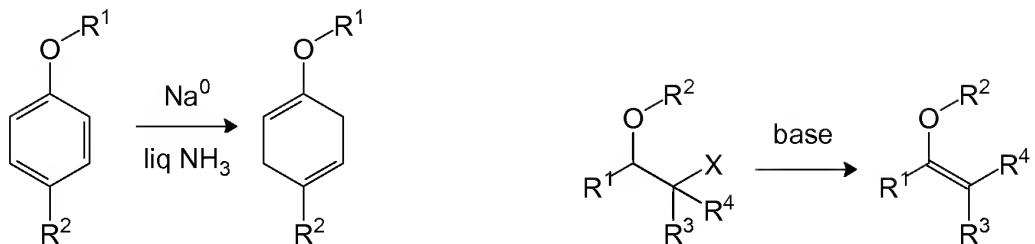


10

Cleavage of an enol ether

15 There are two relatively facile methods for the synthesis of ketone-generation enol ether, although the generation of enol ethers is not limited to these methods and one skilled in the art may find more. One method, metal-liquid ammonia reduction of aromatic compounds, such as phenol ethers, results in the reduction of one carbon-carbon double bond to produce a diene (Birch A.J. *J. Chem. Soc.* **1946**, 593). Another method is the elimination 20 of β -halogen ethers (where chloride, fluoride, bromide, and iodide are halogens) under basic conditions.

Two synthetic strategies for the generation of enol ethers



metal-liquid ammonia reduction

5

elimination of β -chloro ethers
where $X = F, Cl, Br$, or I

An advantage of these methods is that the labile enol ether is produced from relatively stable ethers. This stability of starting material enables one to construct the labile molecule under conditions where it is not labile and then produce the labile enol ether linkage. Using 10 suitable β -haloethers, both methods produce enol ethers that hydrolyze into ketones, which enable one to construct very pH-labile bonds. For example analogs of ethyl isopropenyl ether, which may be synthesized from β -haloethers, have half-lives of roughly 2 minutes at pH 5 (Kresge, A.J.; Sagatys, D.S.; Chen, H.L. *J. Am. Chem. Soc.* **1977**, *99*, 7228). A facile 15 method for the production of a polymer containing isopropenyl ether is the elimination of polyepichlorohydrin under basic conditions (Nishikubo, T., Iizawa, T., Sugarwara, Y., and Shimokawa, T. *J. Polym. Sci., Polym. Chem. Ed.* **1986**, *24*, 1097.) It has been shown (Perez, M., Ronda, J.C., Reina, J.A., Serra, A. *Polymer* **1998**, *39*, 3885.) that reaction of 20 epichlorohydrin with phenolate salts is a competition between substitution, to form the phenol ether, and elimination to form the enol ether. To illustrate the use of elimination of β -haloethers to construct enol ether-containing polyions, we reacted polyepichlorohydrin with 25 the tetrabutylammonium disalt of para-hydroxyphenylacetic acid. The product was a polyanion, due to the substitution reaction, which had enol ether functional groups. This polyanion's ability to form complexes with polyallylamine was lost upon acidification. In addition this enol ether is very pH-labile: measurement of the rate of hydrolysis of the enol ether group by UV spectroscopy revealed a hydrolysis with a half-life of 37 minutes at pH 5.

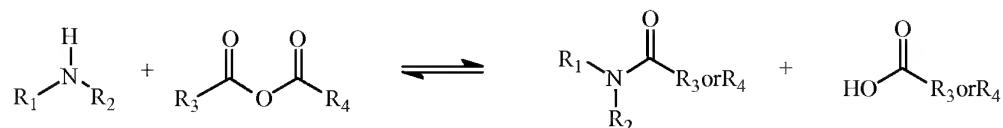
Analogs of ethyl cyclohexenyl ether, which may be synthesized from phenol ethers, have half-lives of roughly 14 minutes at pH 5 (Kresge, A.J.; Sagatys, D.S.; Chen, H.L. *J. Am. Chem. Soc.* **1977**, *99*, 7228). To illustrate this approach to construct enol ethers, we synthesized glycolic acid ethoxylate(4 units) 4-tert-butyl-1,4-cyclohexadiene ether by metal-

liquid ammonia reduction of glycolic acid ethoxylate(4 units) 4-tert-butyl-phenyl ether, which is a phenol ether. The hydrolysis of this enol ether is very acid labile. The half-life of the hydrolysis of this enol ether -containing surfactant was 40 minutes at pH 5.

5 **D. Extremely pH-Labile Bonds**

An illustrative embodiment of the present invention, in which proximity of reactive groups confers lability, is shown by the conversion of amine to amides with anhydrides. Reaction of an amine with an anhydride results in the formation of an amide and a carboxylic acid. As is the case with all chemical reactions, this coupling of amine and anhydride is, in 10 theory, reversible. However, as is the case for many chemical reactions, the reverse reaction (between a carboxylic acid and amide to form an anhydride and amine) is so unfavorable that the reaction between an amine and an anhydride is considered irreversible. Exceptions to this 15 irreversibility are observed when the anhydride is a cyclic anhydride such that the formed amide and acid are in the same molecule, an amide acid. Placement of both reactive groups (amide and carboxylic acid) in the same molecule accelerates their reaction such that amine-anhydride reactivity becomes functionally reversible. For example, the product of succinic 20 anhydride and a primary amine, a succinamic acid, revert back to amine and anhydride 10,000 times faster than the products between noncyclic anhydride and a primary amine. In particular, the product of primary amines with maleic anhydride and maleic anhydride derivatives, maleamic acids, revert back to amine and anhydride with amazing speed, 1×10^9 to 1×10^{13} times faster than its noncyclic analogues (Kirby, AJ. *J. Adv. Phys. Org Chem.* **1980**, 17, 183)

25 Reaction of an amine and an anhydride to form an amide acid.



30 The amide acid that converts to amine and anhydride is the protonated acid, not the deprotonated carboxylate. For this reason, cleavage of the amide acid to form amine and